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Prospects for Measures Against Pollinosis in Japan

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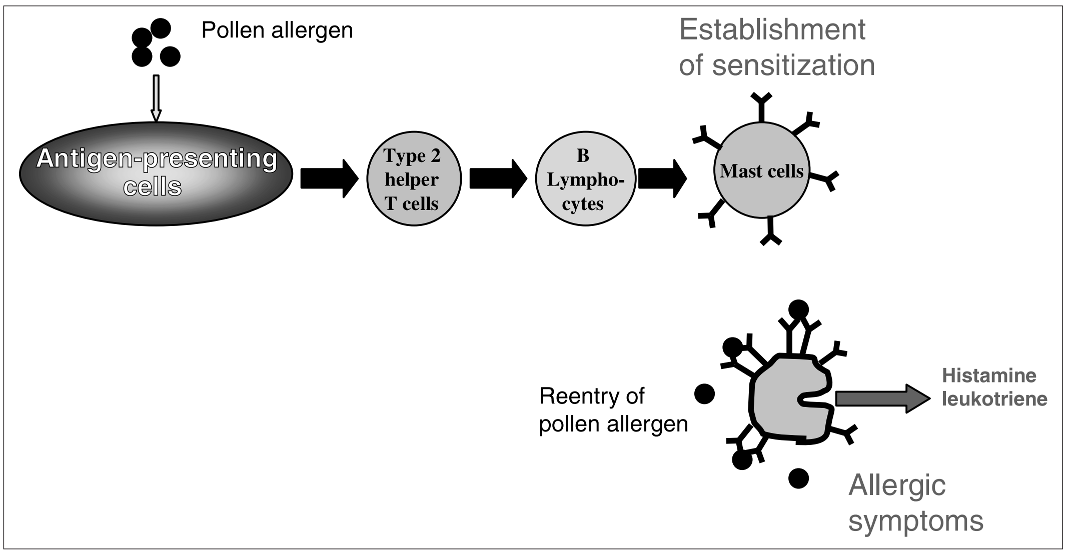
1 Background and Development of Pollinosis Issues

Pollinosis caused by cedar pollens was first reported more than 40 years ago at an academic conference held in 1963. The number of cedar pollinosis *1 patients has increased ever since, and one in every five or six Japanese people is said to suffer from the allergy today. The total medical expenses directly or indirectly related to cedar pollinosis are estimated to reach 286 billion yen per year[1].

The mechanism of pollinosis development is described in Figure 1. First, cells named antigen-presenting cells recognize the allergen (a protein) contained in cedar pollens and transmit its information to type 2 helper (Th2) T cells. Then, the Th2 cells order the B lymphocytes to produce allergen-specific immunoglobulin E (IgE) antibodies. The IgE antibodies bind to the surface of the mast cells, which creates an allergen-sensitized state. When the same allergen enters the body in this state and reacts with the IgE antibodies at the mast cell surface, the mast cells release chemicals such as histamine and leukotriene, which induce allergic symptoms such as sneezing, and running and stuffy noses. Any one of these steps can be blocked in the measures against pollinosis.

Neither sensitization nor allergic reactions would occur in the absence of the allergen, so the fundamental cause of cedar pollinosis is cedar pollen. As shown in Figure 2, Japan's forest cover is 25.12 million ha, corresponding to about 70% of the total land area (37.79 million ha). Planted forests cover 10.36 million ha, which is about 40% of the forest cover. The total area of planted cedar forests is 4.52 million ha, accounting for 18% and 44% of the forest cover and the planted forest area, respectively, while the total area of planted cypress forests is 2.57 million ha, accounting for 10% and 25% of the forest cover and the planted forest area, respectively. Thus, planted forests of cedar and cypress, together, occupy 28% and 19% of the forest cover and the

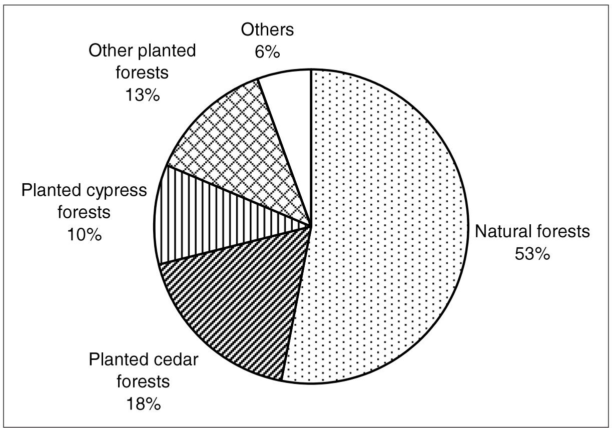
Figure 1 : Diagram of the mechanism of pollinosis development



total land area, respectively. Since most natural forests also comprise broadleaf trees, the actual area occupied by these conifers in natural forests is unknown. Nevertheless, natural forests are also included in addition to the planted forests for the actual calculations. The area of cedar plantation rapidly expanded after World War II and remained at a high level until around 1970. As a result, the majority of the cedar trees are currently aged from 30-50 years[3], as shown in Figure 3. Cedars increase their pollen production at around 25 years and, once they reach 30 years, they constantly produce a large amount of pollen for several decades. The expansion of the area of cedar forests aged over 30 years coincides with the increase in the number of cedar pollinosis patients since 1975[3]. Apparently, the most important factors responsible for the increase of cedar pollinosis are the increased pollen counts in the environment associated with the expansion of cedar and cypress forests, and the resulting increase in the strength and frequency of pollen exposure. Since cedars are expected to live almost 100 years, if the cedar forests are left as they are, we cannot expect any decrease in cedar pollen levels for decades.

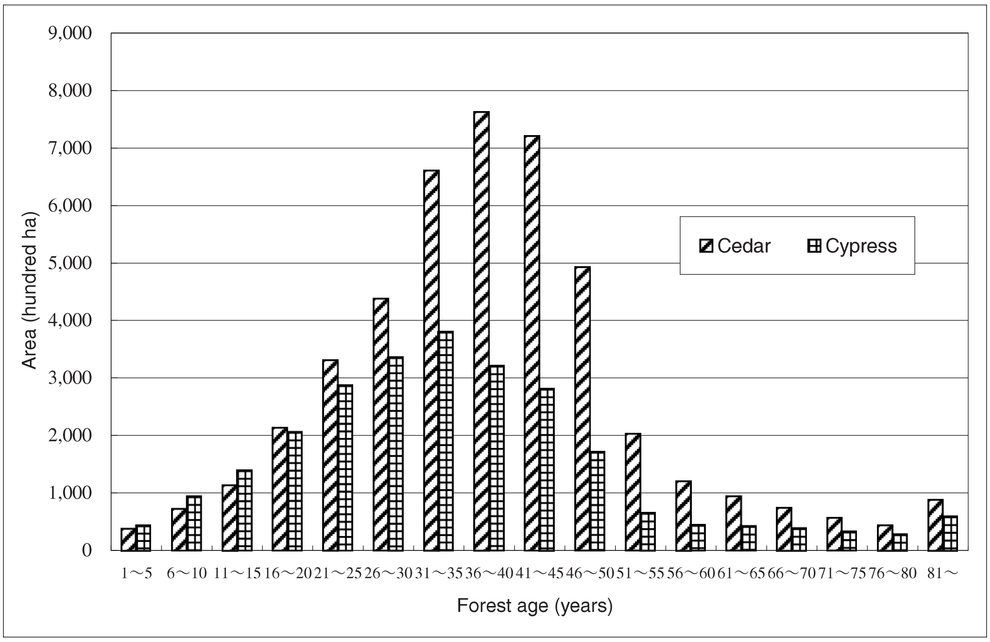
The increase of pollinosis can be viewed as a part of the worldwide increase in allergic diseases which potentially involve various factors including changes in lifestyle, improvements in sanitary conditions, changes in diet, environmental pollution. The involvement of air pollution in pollinosis has been suspected since a higher prevalence was reported among residents along Nikko Kaido, a busy road, than among those living in areas distant from the street, but potentially inhaling a large amount of pollen[4]. Moreover, interesting results were achieved from an animal test, which demonstrated that diesel emissions could exacerbate allergic reactions. Although results from epidemiological studies lack consistency, a survey conducted on elementary students by the Ministry of the Environment demonstrated that the prevalence of cedar-specific IgE antibody and pollinosis were related not only to the pollen count, but also to

Figure 2 : Proportion of planted cedar/ cypress forests in forest cover



Source: Reference [2]

Figure 3 : Areas of planted cedar/ cypress forests by forest age class



Source: Reference [2]

the air pollutant level in the residential area[5]. Many toxicological findings also suggest the involvement of diesel emissions.

2 Past Efforts Concerning Pollinosis Research

Ever since the increase in the cedar pollen count in the environment and the increase in the number of pollinosis patients were first noticed in the 1970s, several studies have been conducted by organizations, including the Ministry of Health, Labour and Welfare (MHLW). In 1975, a study on the airborne pollen count was started utilizing the network of national hospitals and sanitariums and was funded by a MHLW Health Science Research Grant. After that, pollinosis research groups, mainly financed by the MHLW Health Science Research Grant, were organized over several terms. These groups, mainly consisting of otolaryngology and respiratory clinicians, conducted not only epidemiological studies on pollinosis, or clinical and therapeutic research, but also palynological studies such as an airborne pollen survey[6].

Meanwhile, the Forestry Agency approached the cedar pollen issue from a forestry standpoint and started the Cedar Pollen Survey Project in 1987, which involved the investigation of cedar pollen sources in metropolitan areas, surveys on pollen production in cedar forests and related factors, and surveys on cedar pollen dispersion[7].

Through these efforts of the individual ministries and agencies, a committee comprising representatives from relevant ministries and agencies was established in 1990 to investigate and discuss the current status of pollen dispersion and pollinosis as well as the cause of and measures to combat the allergy. From 1997, “Comprehensive Studies towards Overcoming Cedar Pollinosis”, financed by the Special Coordination Funds for Promoting Science and Technology, was conducted over two terms for a total of six years with the cooperation of the related ministries and agencies at the time (Ministry of Education, Science, Sports and Culture, Ministry of Health and Welfare, Forestry Agency, Japan Meteorological Agency, and Environmental Agency)[1].

Apart from the governmental agencies, local governments have also addressed the issue using their own approach. In 1983, the Tokyo Metropolitan Government launched a study group on measures against pollinosis and started cedar pollen count measurements and patient surveys, which have continued ever since. Other prefectures have cooperated with the local medical associations, universities, etc. and played pioneering roles in the establishment of systems for measuring pollen counts or providing information to the residents. In Japan, cedar pollens have been manually counted using a traditional method called the Durham method. For many years, the method was supported by doctors, researchers from various fields, and citizen volunteers. Today, an NPO group, Pollen Information Association, plays the central role.

3 Current Status of Measures Against Pollinosis

In February 2004, the Council for Science and Technology Policy established a Research Committee on Measures Against Pollinosis comprising executives from relevant ministries and agencies, and experts on pollinosis to promote studies on measures to combat pollinosis. The committee announced “Governmental Efforts Concerning Pollinosis for This Term”[8] and suggested some specific policies shown in Table 1.

Among such efforts, those directly related to the measures against pollinosis can be broadly classified into pollen source control, exposure reduction, and prevention and treatment.

(1) Pollen source control

Control of cedar and cypress forests serving as pollen sources is the most basic countermeasure against pollinosis. The pollen source control policies currently promoted by the Ministry of Agriculture, Forestry, and Fisheries (MAFF) are (i) development and spread of low-pollen varieties etc., and (ii) logging and thinning of trees producing many male flowers. The development of low-pollen cedar varieties producing less than 1% of normal pollen production has been somewhat successful, supplying about 240

Table 1 : Efforts concerning measures against pollinosis

Program	Item	Relevant ministries and agencies
Understanding of current status regarding pollen and pollinosis	(i) Prediction of pollen production	MAFF
	(ii) Weather forecast, etc.	Japan Meteorological Agency
	(iii) Forecast and monitoring of the pollen count	Ministry of the Environment
Identification of the cause of pollinosis	(i) Identification of the disease mechanism	MEXT/MHLW
	(ii) Identification of the relationship between pollinosis and general environment	Ministry of the Environment
	(iii) Establishment of a research base	MEXT/MHLW
Measures against pollinosis	(i) Development and spread of preventive and therapeutic methods	MEXT/MHLW
	(ii) Development and spread of low-pollen varieties etc.	MAFF
	(iii) Promotion of logging and thinning of trees producing many male flowers	MAFF
	(iv) Securing appropriate medical service for pollinosis	MHLW
	(v) Provision of information concerning pollen and pollinosis	MHLW/MAFF/Ministry of the Environment

thousand low-pollen trees over the past five years and potentially supplying about 600 thousand over the next five years[3].

(2) Reduction and avoidance of exposure

This class of policies involves the reduction or avoidance of exposure to cedar pollens at any of the stages including pollen production, pollen dispersion in the environment, and human exposure to pollens.

Cedar pollen dispersion is a seasonal phenomenon, so it is important to predict the beginning and end of pollen dispersion. It is also important to predict the total pollen count that greatly varies from year to year. Since anti-allergic drugs are commonly used as the initial drugs administered about two weeks before the pollen dispersion begins, an increase in prediction accuracy at the beginning of pollen dispersion is critical to appropriate treatment, as well as to reducing medical costs and the patient burden.

Another means for reducing exposure to pollens is to reduce opportunities for contact with pollen or to avoid activities that would result in contact with pollen. Pollen forecasts for today and tomorrow, provided as a part of the weather forecast, are critical to the selection of one's activities to avoid pollen exposure. A forecast system for a shorter term, e.g. an hourly forecast, would require pollen production data and meteorological data with the equivalent temporal resolution. In fiscal year 2002, the Ministry of the Environment placed automatic pollen counters in urban and mountain areas in the Kanto, Kansai, and Chubu regions and started to collect and provide hourly data on pollen dispersion. The ministry will eventually place the pollen counters all around the country. Cedar pollens are believed to travel several dozen kilometers, so a pollen dispersion model that covers a wide area is needed. For example, the establishment of a pollen prediction model for Tokyo would require data collected from the entire Kanto region.

(3) Prevention and treatment

Pollinosis can be prevented or treated by blocking any of the several stages shown in Figure 1. The most fundamental form of prevention is to avoid contact with pollen. Meanwhile, another preventive approach is to suppress the allergic reactions developed after contact with pollen in a sensitized subject, in which pollen-specific IgE antibodies are produced and bound to the surface of the mast cells. The latter involves suppression of the allergic symptoms in patients who have already developed pollinosis, so it is difficult to draw a clear distinction between prevention and treatment.

Currently, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and MHLW are focusing on research and development of cedar pollen CpG vaccines and sublingual desensitization (Figure 4). Meanwhile, MAFF is promoting the development of pollinosis-relieving rice (Figure 5). These

Figure 4 : Road map for development of therapeutic methods promoted by MEXT and MHLW

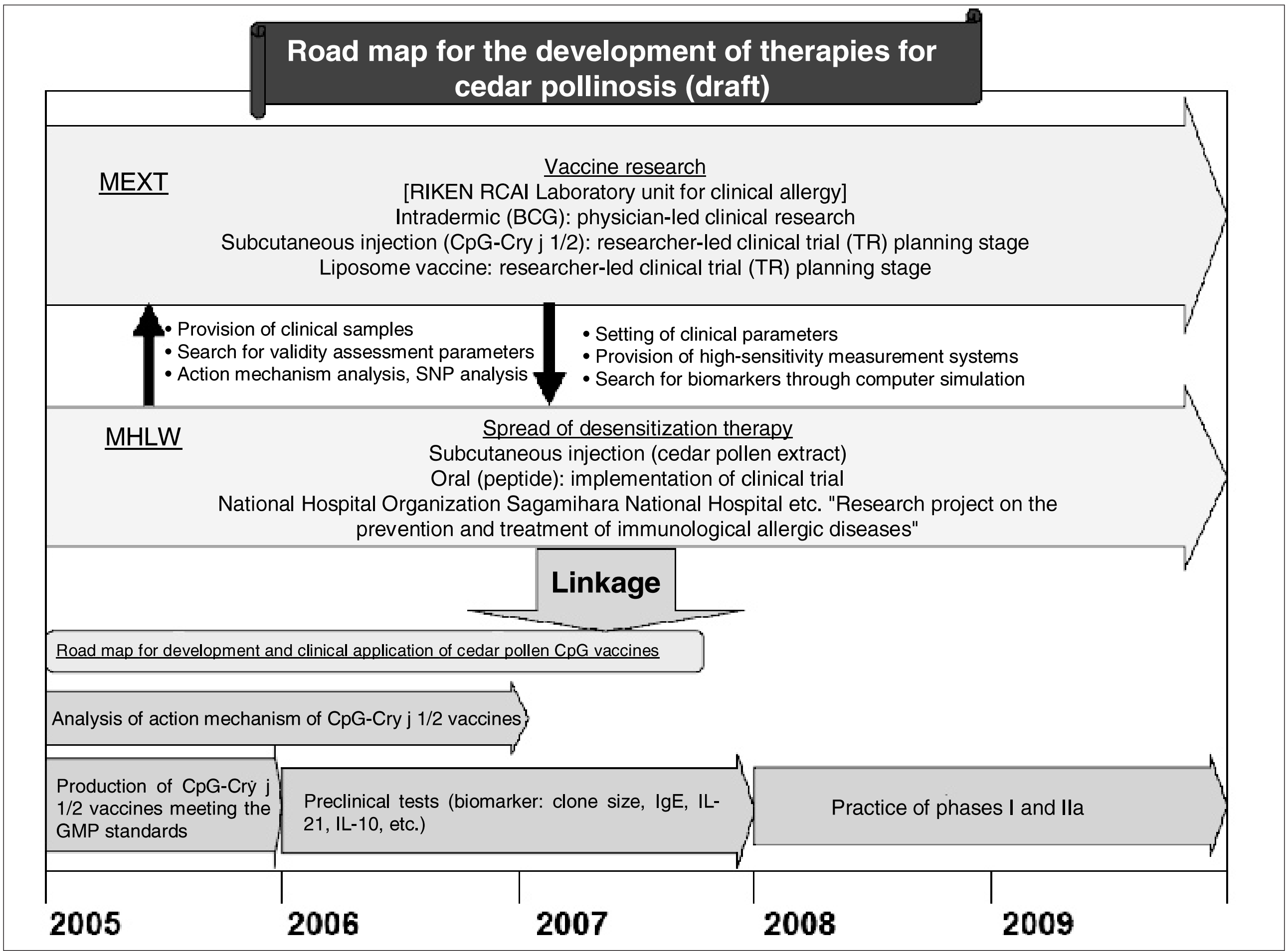
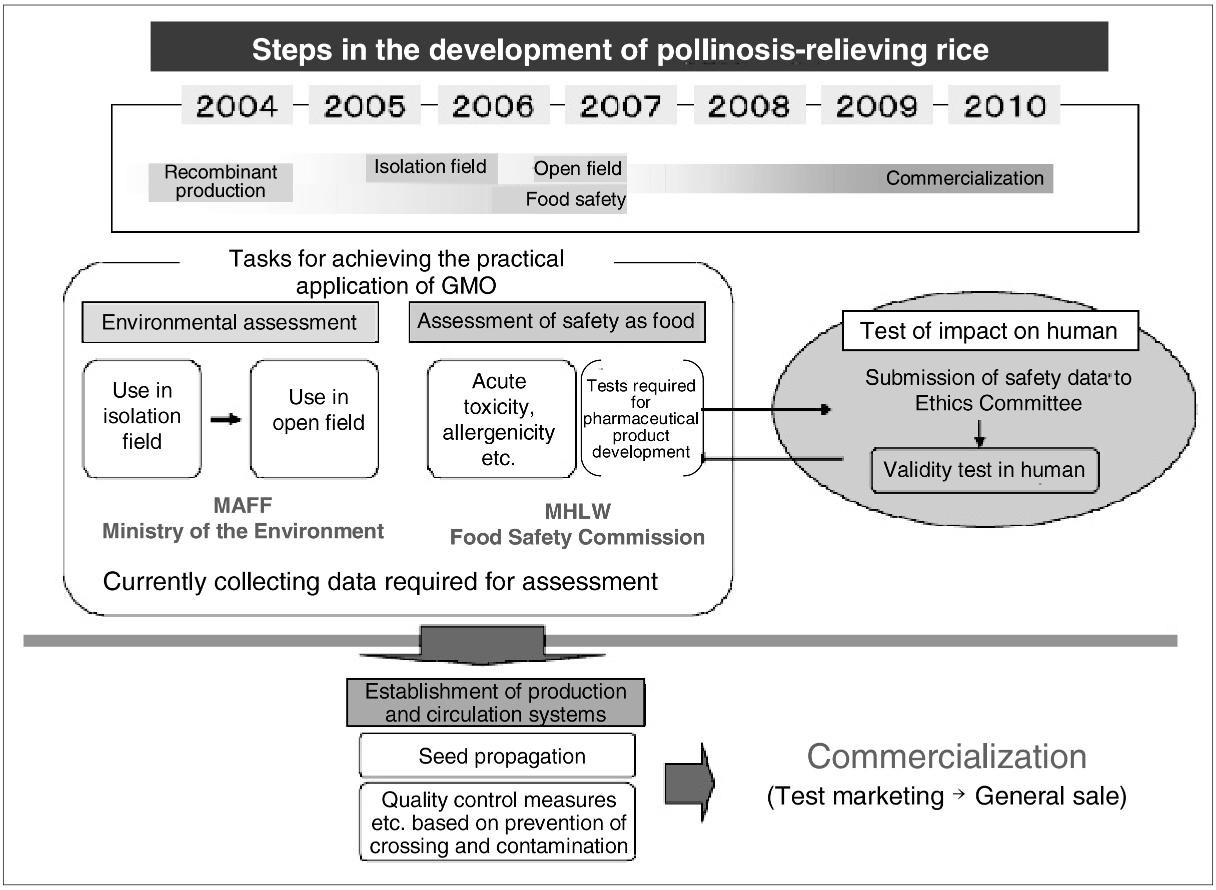


Figure 5 : Road map for the development of pollinosis-relieving rice promoted by MAFF



prevention and treatment methods are extensions of a therapy called desensitization therapy and can be classified as curative treatments, which can be distinguished from symptomatic treatments based on anti-allergic drugs. Such curative treatments seem to be the most promising measures against pollinosis.

Desensitization therapy is an allergen-specific immunotherapy involving the routine injection of cedar pollen extracts over two or three years, starting with low doses and acclimatizing the body to the allergen to suppress the allergic symptoms. This method has been commonly used in the U.S. and European countries but has been rather rare Japan, due to some disadvantages such as the need for several hospital visits over long periods and a low but non-negligible risk of allergy shock. Among the stages for the establishment of sensitization shown in Figure 1, the immunotherapy under study suppresses the action of Th2 cells or B lymphocytes to reduce pollen-specific IgE antibody production.

The use of cedar pollen-specific CpG vaccines involves suppression of the cedar-specific Th2 cells by administering the major protein components of the cedar pollen allergen, Cry j 1 and Cry j 2, bound to bacterial or microbial DNA fragments (unmethylated CpG motifs) known to have strong immunostimulatory activities. In the U.S., their counterparts containing ragweed pollen allergens instead of cedar pollen allergens, have been tested in clinical trials and demonstrated to be effective against ragweed pollinosis. The efficacy of cedar pollen CpG vaccines has already been confirmed in mice, and preparations for their clinical trials are currently in progress. Once their efficacy and safety are confirmed through the clinical trials, the vaccines will be put into practical use two or three years after the beginning of the clinical trials.

Unlike conventional desensitization through injection, sublingual desensitization achieves desensitization by dropping pollen extract under the tongue (or, generally, by placing a piece of bread impregnated with the pollen extract under the tongue for about two minutes). The method has already been approved in Europe, and a large amount of data showing its efficacy is available.

The pollinosis-relieving rice is rice that has been genetically modified to accumulate a peptide considered to prevent cedar pollinosis in the endosperm. The peptide contains a peptide (7Crp) consisting of seven linked major antigenic determinants (T-cell epitopes) of cedar allergens recognized by human T cells among the known T-cell epitopes. The gene encoding the peptide is further linked to some genes required for gene transfer. The rice containing the pollinosis-preventing peptide is approved for use etc. in isolated fields under the Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Cartagena Law). In the road map provided by MAFF, the rice will be first subjected to environmental and food safety assessment, followed by confirmation of its efficacy in humans, before it is put into practical use.

4 Future Directions of Measures Against Cedar Pollinosis

4-1 More effective control of pollen sources and evaluation of its validity

For more effective control of pollen sources, closer linkages must be established between pollen source control and the development of a pollen forecast system promoted by MAFF/ Forestry Agency and the Ministry of the Environment/ Japan Meteorological Agency, respectively. A map illustrating the degree of contribution of cedar/ cypress forests in Japan to the pollen exposure of population groups needs to be produced, and the cedar/ cypress forests must be prioritized as targets for pollen source control. Moreover, the cost and the manpower required for the control must be estimated, and a road map for the entire policy must be produced.

Under existing conditions, it is difficult to predict the decrease in the sensitization rate from the predicted decrease in the pollen count as a result of pollen source control conducted in cedar/ cypress forests in a certain area. Thus, it is essential to promote studies on the relationship between pollen exposure and allergic reactions to pollens.

(1) Cost and manpower required for pollen source control

Application of the pollen source control promoted by the MAFF/ Forestry Agency to the vast area of cedar/ cypress forests would require a huge commitment in manpower and money, but neither has been clearly estimated. In the budget for the fiscal year 2005, 250 billion yen was allocated for the development and maintenance of 6.4 million ha of forest as a part of the global warming policy. The forest development cost related to cedar pollinosis control would perhaps be equivalent to this, or even higher. Meanwhile, forestry workers in our country have become older and decreased in number to about one-third of that 30 years ago (Figure 6). It is unclear whether there would be enough manpower to practice forest development and maintenance as a part of cedar pollen source control.

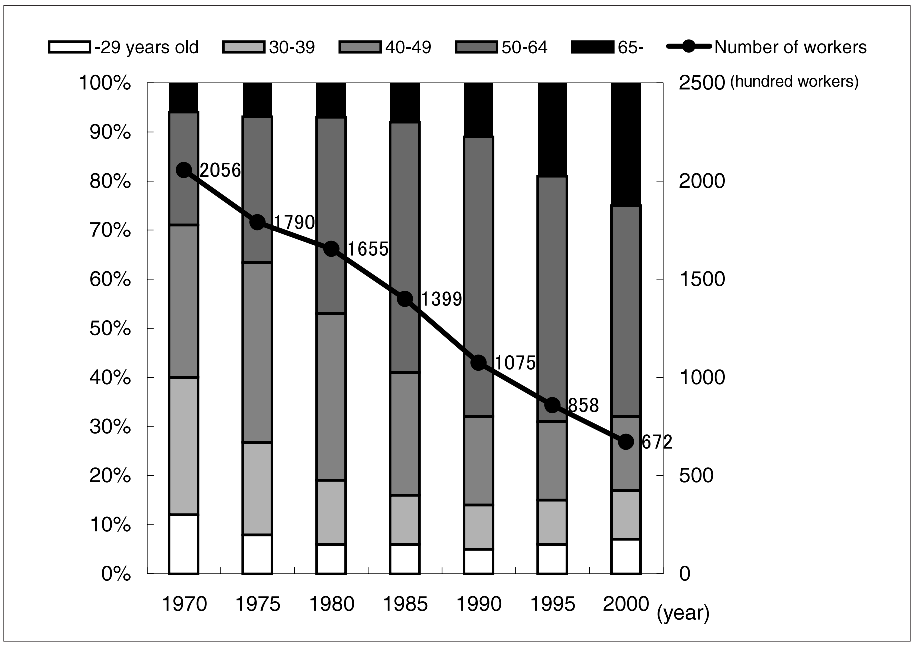
(2) Prioritization of target areas for control based on estimation

Although the existing trees should be replaced with those producing less or no pollen, and trees producing many male flowers should be logged or thinned, it is unrealistic to work on all of the vast cedar/ cypress forests at once. Thus, the first thing to do is an individual estimation of the degree of contribution of cedar/ cypress forests to the pollen exposure of population groups in each area of the country, followed by prioritization of the forests. For instance, it is necessary to identify cedar/ cypress forests that are making the largest contribution to the heavily populated metropolitan areas. The determination of the priority should be followed by an estimation of the funds and manpower required for the policy and the establishment of a road map for the entire policy. Accomplishment of these tasks would require the establishment of a cedar pollen forecast model including a system for predicting cedar pollen production and dispersion, a system for predicting the airborne pollen count described in 4-1(3), and a weather observation/ forecast system serving as its basis. In addition, the prioritization should be performed by taking into account the important functions of the forests from the standpoints of land conservation and prevention of global warming, such as their roles as CO_2 sinks and watershed protection forests.

(3) Accumulation of observation data and the improvement of accuracy

Since cedar pollens are believed to travel several dozen kilometers, a pollen forecast model that covers a wide area needs to be established. Moreover, considering the flow rate of pollens in the atmosphere, the observation data should be collected on an hourly basis. Unfortunately, the currently available observation data on

Figure 6 : Transition of the number of forestry workers and composition ratio according to their age



spatial and temporal pollen distribution are inadequate. Airborne pollen counts were conventionally measured through an approach called the Durham method, in which pollens deposited on a slide glass are stained and counted under an optical microscope. In the Durham method, observations are usually made on a daily basis, making it difficult to establish an hourly prediction system based on the observation data obtained through this method. Currently, real-time data on pollen production in cedar forests serving as cedar pollen sources are virtually unavailable. The monitoring system developed by the Ministry of the Environment has only a limited number of monitoring sites, and a fundamental discussion on the number and the location of monitoring sites would be required to increase the accuracy of the pollen forecast system. Furthermore, since the existing automatic pollen counters are not designed as cedar pollen-specific counters but are merely particle counters that count any particles of the same size as cedar pollens, errors may be observed under certain conditions. Thus, the system and accuracy of the pollen counter itself needs to be improved.

Currently, the prediction of the total pollen count for the year is performed based on the flower setting of the male cedar flowers and is available before the cedar pollen season, i.e. around November or December. Cedar flower buds are formed in the summer, and their formation is affected by weather conditions in the summer. Based on this fact, a statistical prediction system based on summer temperature etc. had been proposed. However, since other factors are also involved in flower bud formation, predictions based only on the summer temperature or other weather conditions produced some errors. Consequently, the total pollen count has been predicted based on the observation of the male flowers in autumn when they show a marked growth and prediction accuracy has increased in recent years.

On the other hand, predictions of the onset and end of pollen dispersion are not sufficiently accurate. In particular, the onset is linked to the initiation of drug administration, so it should be predicted with an accuracy of a few days. Cedar male flowers stop growing in autumn and enter dormancy. The onset of pollen dispersion is predicted by analyzing the meteorological factors involved in dormancy breaking. However, the mechanism of dormancy breaking is not sufficiently understood, and fundamental studies are needed to increase prediction accuracy.

(4) Establishment of a method for evaluating the impact of measures

Many problems are left unsolved concerning the evaluation of the impact of the measures. As mentioned earlier, the development of pollinosis comprises two stages, i.e. sensitization and symptom development, but the dose-effect relationship has not been clearly established for either of the steps. In particular, there are no collective data on the relationship between the degree of pollen exposure and the sensitization rate in certain population groups with a genetic predisposition. Thus, it is difficult to predict sensitization rate reduction from the predicted reduction in the pollen count resulting from pollen source control in cedar/ cypress forests. Meanwhile, there are some findings on the degree of pollen exposure (pollen count) during the pollen dispersion season that triggers the allergic symptoms in a person already developing pollinosis. These findings have been used for ranking cedar pollen dispersion in the forecast. Although such ranking is not reliable enough to accurately evaluate the impact of measures, at least for the time being, there is no choice but to use the development of allergic symptoms as a measure of the impact. Elucidation of the dose-effect relationship between pollen exposure and its outcome requires reinforcement of the pollen monitoring network and continuation of epidemiological surveys on young people at ages that are critical to the establishment of sensitization.

4-2 Solutions for problems concerning prevention and treatment

The results of high priority basic research on the new preventive and therapeutic methods currently in progress, such as vaccine development and sublingual immunotherapy, suggest that these methods have a high potential for practical application. In the future, they need to be tested in clinical trials to be approved as pharmaceutical drugs, which would require some research support. Joint developments with pharmaceutical companies etc. would be essential for their practical application, and problems that may arise during such joint developments should be clarified in advance.

(1) Support for research and clinical trials

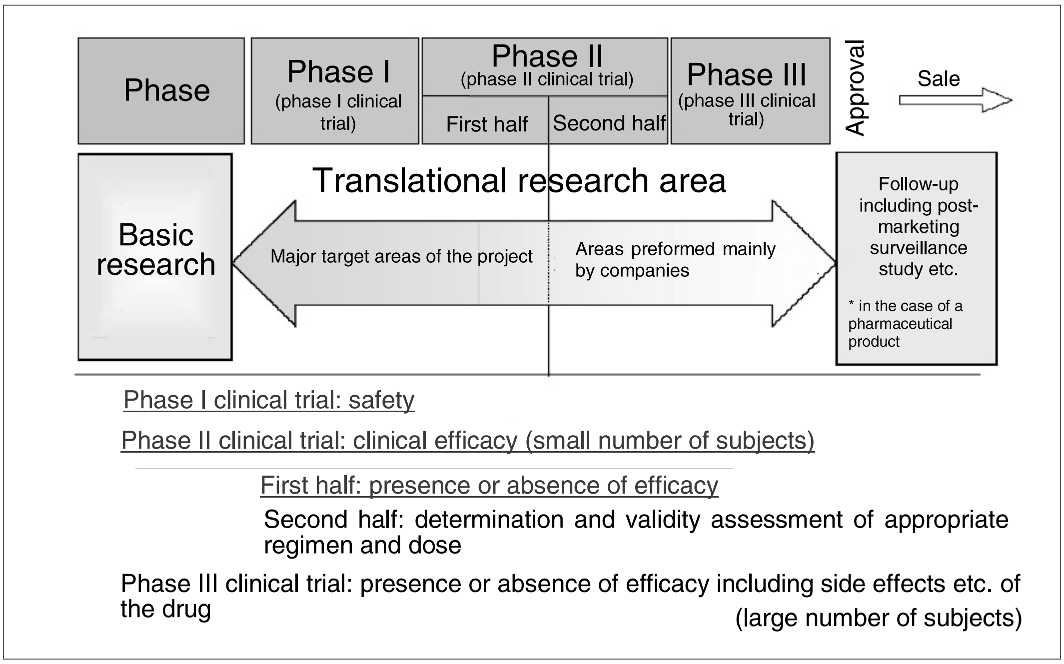
In order to put the currently developed preventive and therapeutic methods into practice as soon as possible, it is essential to provide both research support for basic studies on the immune system and allergies, and practical support for clinical trials. Research performed for developing and commercializing promising diagnostic, therapeutic, or preventive methods based on the results achieved through basic studies in the life sciences and returning the outcome to the patients is called translational research. The development of cedar pollen vaccines is a good example of translational research. In cancer research, MEXT started the "Cancer Translational Research Project"[11] in fiscal year 2004 (Figure 7). This project targets phase I and the first half of phase II of clinical trials, and the Foundation for Biomedical Research and Innovation (Translational Research Informatics Center) provides some support for the preparation of clinical study protocols, management, and statistical analysis of clinical data, etc. Meanwhile, concerning the second half of phase II and phase III clinical trials, the basic policies of the project state "(the target research) shall be feasible, e.g. phases II and III of clinical trials shall be taken over by companies etc.", which assumes that companies such as pharmaceutical companies, that would benefit from the practical application, will bear the costs of clinical trials, and work on approval procedures. The development of cedar pollen vaccines would require similar support.

In a review[12] summarizing 100 reports on sublingual immunotherapy, Cox claimed that, although the method was effective in relieving symptoms and reducing the doses of the therapeutic drugs, there were some questions about the effective dose and schedule, timing, mode of action, and safety in hypersensitive groups. More clinical data should be gathered to optimize the dose and administration method of the allergen, and the efficacy and safety of cedar pollen allergen extract should be evaluated as soon as possible to achieve early approval of the vaccine.

(2) Promotion of vaccine development etc.

The results of basic research on vaccines preventing the development of cedar pollinosis,

Figure 7 : Cancer Translational Research Project



Source: Reference [11]

such as CpG vaccines, suggest that these vaccines have a high potential for practical application. However, drug development is often associated with many problems that have led to the cessation of clinical trials and the failure of many drugs to reach commercialization in the past. The development of such vaccines would also be confronted by many problems that need to be solved. As can be seen from the example of the Cancer Translational Research Project, it is beyond the capacity of individual researchers or research institutions to complete all phases of the clinical trials, achieve governmental approval, and reach commercialization. Yet, the government can only make a limited commitment to the implementation of clinical trials. This problem can only be solved through joint development with pharmaceutical companies etc. The cooperation of pharmaceutical companies is also vital for the development of sublingual desensitization, as pollen extracts that are different from those approved for injection use would need to be newly approved under the Pharmaceutical Affairs Law.

(3) Safety confirmation of pollinosis-relieving rice

Since pollinosis-relieving rice is based on an innovative idea, a highly advanced assessment on procedures of safety and efficacy evaluation is required. The rice would also be confronted by many problems. Following the procedures for environmental assessment of genetically modified crops specified in the Cartagena Law, the next task concerning the rice containing the pollinosis-preventing peptide is to achieve approval for its cultivation in open fields[13]. Regarding the assessment of its safety as food, the Food Safety Commission has established standards for safety assessments of genetically modified foods[14]. Thus, if the rice containing the pollinosis-preventing peptide is viewed only as a genetically modified food, well-defined procedures are already in place for its environmental and food safety evaluation. However, for the practical application of peptide vaccines or other immunotherapy methods using 7Crp itself, their efficacy and safety as pharmaceutical products must be assessed under the Pharmaceutical Affairs Law. Consequently, if the rice is viewed as a pharmaceutical product, it must undergo all phases of the clinical trials shown in Figure 7. Moreover, it would have to overcome the negative views of consumers about genetically modified foods in general.

5 Conclusion

The present article focused on cedar/ cypress pollinosis and provided an outlook of the prospects for measures to combat this problem, which is of national concern. A substantially high incidence is reported for other types of pollinosis caused by, for example, Gramineae pollens, although conditions for their development are not fully understood due to the limited range of pollen dispersion, etc. The involvement of environmental pollution such as air pollution in pollinosis is often highlighted, but environmental pollution seems to be involved in all other allergic conditions as well. A drastic increase of allergic diseases has been observed worldwide, although the increase in cedar pollinosis seems to have a history that is unique to our country. Nevertheless, before starting individual research, first we must clearly define the position of the measures against cedar pollinosis in the prevention and treatment of allergic conditions in general.

Glossary

*1 Cedar pollinosis

Otherwise known as cedar/ cypress pollinosis, as most cedar pollinosis patients develop allergic symptoms in response to cypress pollens as well as cedar pollens. Unless there is a need, this article does not distinguish between cedar pollinosis and cypress pollinosis.

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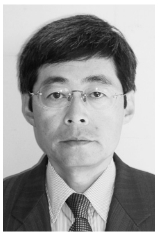

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